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Non-Small Cell **Lung Cancer** (PDQ®): Treatment

General Information About Non-Small Cell Lung Cancer

Key Points for This Section

- Non-small cell **lung cancer** is a disease in which malignant (**cancer**) cells form in the tissues of the **lung**.
- There are several types of non-small cell **lung cancer**.
- Smoking can increase the risk of developing non-small cell **lung cancer**.
- Possible signs of non-small cell **lung cancer** include a cough that doesn't go away and shortness of breath.
- Tests that examine the lungs are used to detect (find), diagnose, and stage non-small cell **lung cancer**.
- Certain factors affect prognosis (chance of recovery) and treatment options.
- For most patients with non-small cell **lung cancer**, current treatments do not **cure** the **cancer**.

Non-small cell lung cancer is a disease in which malignant (cancer) cells form in the tissues of the lung.

The lungs are a pair of cone-shaped breathing organs in the chest. The lungs bring oxygen into the body as you breathe in. They release carbon dioxide, a waste product of the body's cells, as you breathe out. Each **lung** has sections called lobes. The left **lung** has two lobes. The right **lung** is slightly larger and has three lobes. Two tubes called bronchi lead from the trachea (windpipe) to the right and left lungs. The bronchi are sometimes also involved in **lung cancer**. Tiny air sacs called alveoli and small tubes called bronchioles make up the inside of the lungs.

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Español

Questions about cancer?
- **1-800-4-CANCER**
- LiveHelp® online chat
- E-mail

NCI Highlights

NCI Creates Clinical Proteomic Technology Centers

TCGA to Study **Lung**, Brain, and Ovarian Cancers

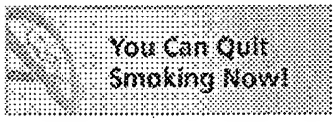
The Nation's Investment in **Cancer** Research FY 2008

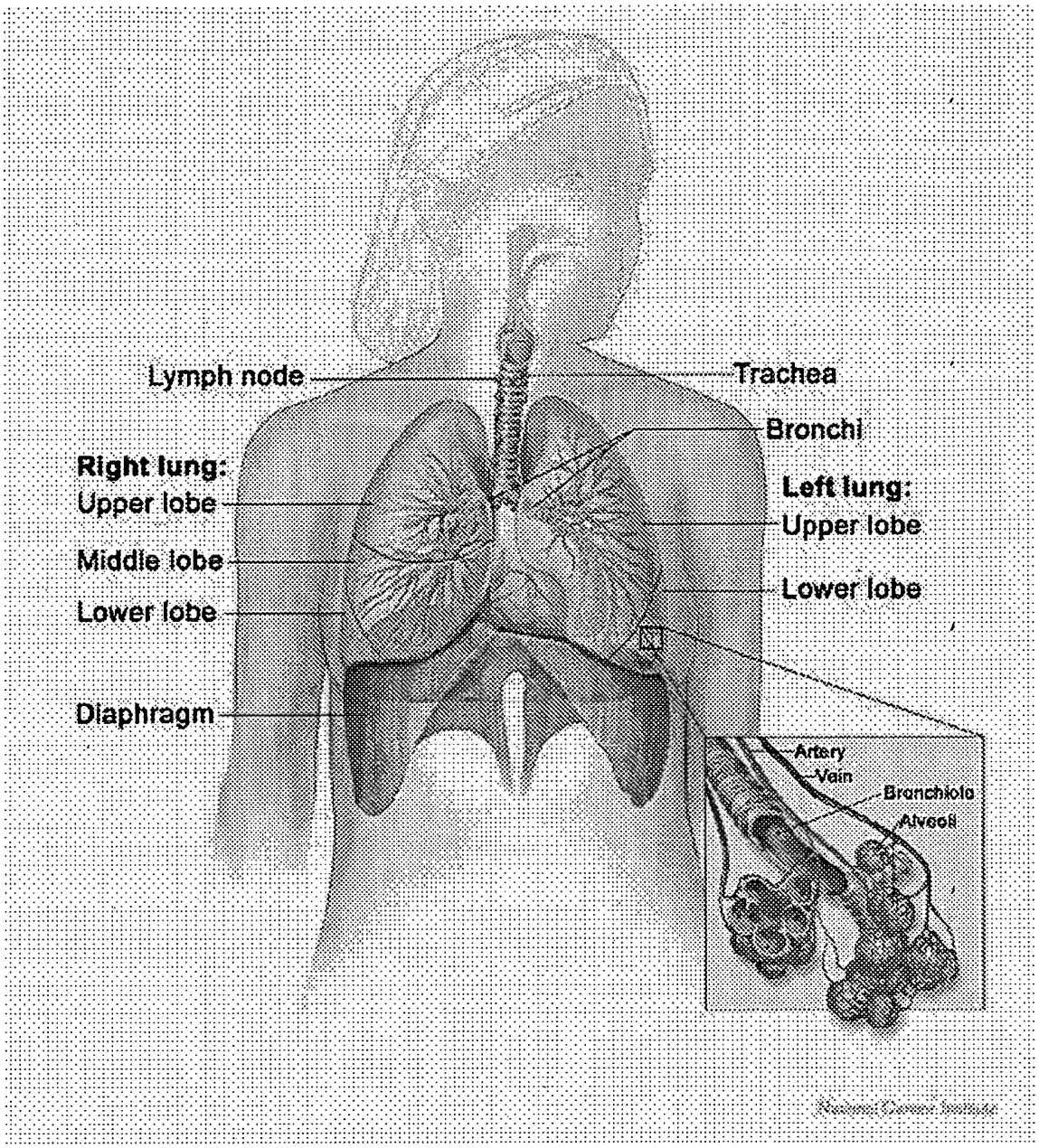
Statement on Fiscal Year 2007 Budget Request

Cancer Trends Progress Report: 2005 Update

NCAB Working Group Report on Biomedical Technology

Past Highlights





Anatomy of the respiratory system, showing the trachea and both lungs and their lobes and airways. Lymph nodes and the diaphragm are also shown. Oxygen is inhaled into the lungs and passes through the thin membranes of the alveoli and into the bloodstream (see inset).

A thin membrane called the pleura covers the outside of each **lung** and lines the inside wall of the chest cavity. This creates a sac called the pleural cavity. The pleural cavity normally contains a small amount of fluid that helps the lungs move smoothly in the chest when you breathe.

There are two main types of **lung cancer**: non-small cell **lung cancer** and small cell **lung cancer**. (See the PDQ summary on Small Cell **Lung Cancer** Treatment for more information.)

There are several types of non-small cell lung cancer.

Each type of non-small cell **lung cancer** has different kinds of **cancer** cells. The **cancer** cells of each type grow and spread in different ways. The types of non-small cell **lung cancer** are named for the kinds of cells found in the **cancer** and how the cells look under a microscope:

- Squamous cell carcinoma: **Cancer** that begins in squamous cells, which are thin, flat cells that look like fish scales. This is also called epidermoid carcinoma.
- Large cell carcinoma: **Cancer** that may begin in several types of large cells.
- Adenocarcinoma: **Cancer** that begins in the cells that line the alveoli and make substances such as mucus.

Other less common types of non-small cell **lung cancer** are: pleomorphic, carcinoid tumor, salivary gland carcinoma, and unclassified carcinoma.

Smoking can increase the risk of developing non-small cell lung cancer.

Smoking cigarettes or cigars is the most common cause of **lung cancer**. The more years a person smokes, the greater the risk. If a person has stopped smoking, the risk becomes lower as the years pass, but is never completely gone.

Anything that increases a person's chance of developing a disease is called a risk factor. Risk factors for **lung cancer** include the following:

- Smoking cigarettes or cigars, now or in the past.
- Being exposed to second-hand smoke.
- Being treated with radiation therapy to the breast or chest.
- Being exposed to asbestos, radon, chromium, arsenic, soot, or tar.
- Living where there is air pollution.

When smoking is combined with other risk factors, the risk of developing **lung cancer** is increased.

Possible signs of non-small cell lung cancer include a cough that doesn't go away and shortness of breath.

Sometimes **lung cancer** does not cause any symptoms and is found during a routine chest x-ray. Symptoms may be caused by **lung cancer** or by other conditions. A doctor should be consulted if any of the following problems occur:

- A cough that doesn't go away.
- Trouble breathing.
- Chest discomfort.
- Wheezing.
- Streaks of blood in sputum (mucus coughed up from the lungs).
- Hoarseness.
- Loss of appetite.
- Weight loss for **no** known reason.
- Feeling very tired.

Tests that examine the lungs are used to detect (find), diagnose, and stage non-small cell lung cancer.

Tests and procedures to detect, diagnose, and stage non-small cell **lung cancer** are often done at the same time. The following tests and procedures may be used:

- Physical exam and history: An exam of the body to check general signs of health, including checking for signs of disease, such as lumps or anything else that seems unusual. A history of the patient's health habits, including smoking, and past jobs, illnesses, and treatments will also be taken.
- Chest x-ray: An x-ray of the organs and bones inside the chest. An x-ray is a type of energy beam that can go through the body and onto film, making a picture of areas inside the body.

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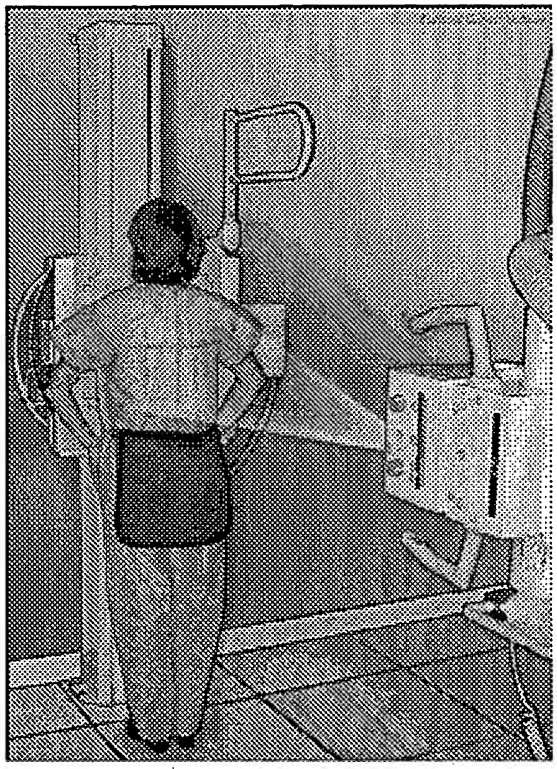

X-ray of the chest. X-rays are used to take pictures of organs and bones of the chest. X-rays pass through the patient onto film.

- CT scan (CAT scan): A procedure that makes a series of detailed pictures of areas inside the body, such as the chest, taken from different angles. The pictures are made by a computer linked to an x-ray machine. A dye may be injected into a vein or swallowed to help the organs or tissues show up more clearly. This procedure is also called computed tomography, computerized tomography, or computerized axial tomography.
- PET scan (positron emission tomography scan): A procedure to find malignant tumor cells in the body. A small amount of radionuclide glucose (sugar) is injected into a vein. The PET scanner rotates around the body and makes a picture of where glucose is being used in the body. Malignant tumor cells show up brighter in the picture because they are more active and take up more glucose than normal cells do.

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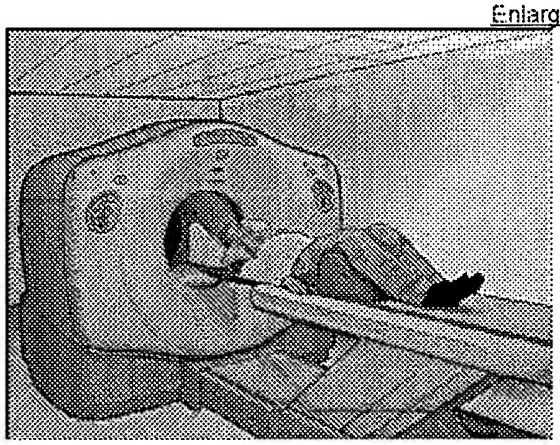

PET (positron emission tomography) scan. The patient lies on a table that slides through the PET machine. The head rest and white strap help the patient lie still. A small amount of radioactive glucose (sugar) is injected into the patient's vein, and a scanner makes a picture of where the glucose is being used in the body. **Cancer** cells show up brighter in the picture because they take up more glucose than normal cells do.

- Sputum cytology: A procedure in which a pathologist views a sample of sputum (mucus coughed up from the lungs) under a microscope, to check for **cancer** cells.

- Fine-needle aspiration biopsy of the **lung**: The removal of part of a lump, suspicious tissue, or fluid from the **lung**, using a thin needle. This procedure is also called needle biopsy. Ultrasound or another imaging procedure is used to locate the abnormal tissue or fluid in the **lung**. A small incision may be made in the skin where the biopsy needle is inserted into the abnormal tissue or fluid. A sample is removed with the needle and sent to the laboratory. A pathologist then views the sample under a microscope to look for **cancer** cells. A chest x-ray is done after the procedure to make sure **no** air is leaking from the **lung**.
- Bronchoscopy: A procedure to look inside the trachea and large airways in the **lung** for abnormal areas. A bronchoscope (a thin, lighted tube) is inserted through the nose or mouth into the trachea and lungs. Tissue samples may be taken for biopsy.

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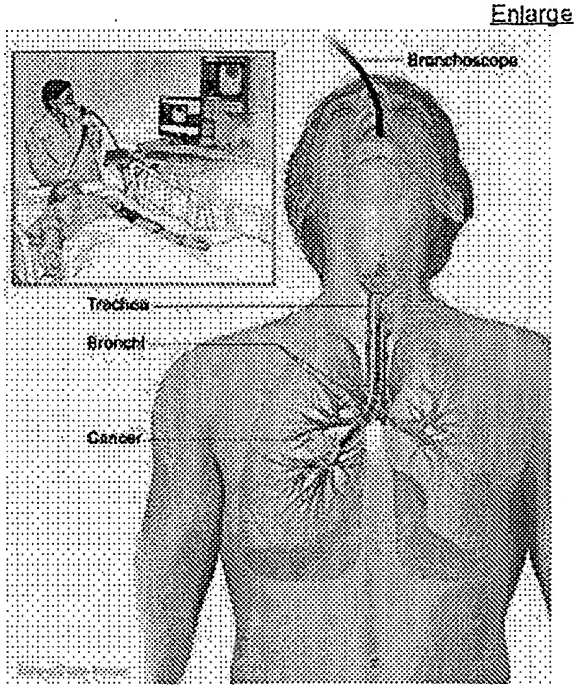

Bronchoscopy. A bronchoscope is inserted through the mouth, trachea, and major bronchi into the **lung**, to look for abnormal areas. A bronchoscope is a thin, tube-like instrument with a light and a lens for viewing. It may also have a cutting tool. Tissue samples may be taken to be checked under a microscope for signs of disease.

- Thoracoscopy: A surgical procedure to look at the organs inside the chest to check for abnormal areas. An incision (cut) is made between two ribs, and a thoracoscope (a thin, lighted tube) is inserted into the chest. Tissue samples and lymph nodes may be removed for biopsy. This procedure may be used to remove parts of the esophagus or **lung**. If certain tissues, organs, or lymph nodes can't be reached, a thoracotomy may be done. In this procedure, a larger incision is made between the ribs and the chest is opened.
- Thoracentesis: The removal of fluid from the space between the lining of the chest and the **lung**, using a needle. A pathologist views the fluid under a microscope to look for **cancer** cells.

Certain factors affect prognosis (chance of recovery) and treatment options.

The prognosis (chance of recovery) and treatment options depend on the following:

- The stage of the **cancer** (the size of the tumor and whether it is in the **lung** only or has spread to other places in the body).
- The type of **lung cancer**.
- Whether there are symptoms such as coughing or trouble breathing.
- The patient's general health.

For most patients with non-small cell lung cancer, current treatments do not cure the cancer.

If **lung cancer** is found, taking part in one of the many clinical trials being done to improve treatment should be considered. Clinical trials are taking place in most parts of the country for patients with all stages of non-small cell **lung cancer**. Information about ongoing clinical trials is available from the NCI Web site.

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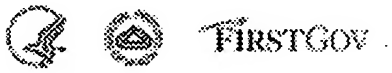

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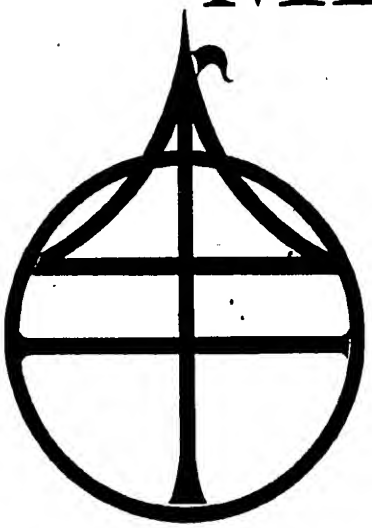

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PART XIV

ONCOLOGY

154 INTRODUCTION

Joseph V. Simone

BACKGROUND

DEFINITIONS, INCIDENCE, AND MORTALITY. Cancer describes a class of diseases characterized by the uncontrolled growth of aberrant cells. Cancers kill by the destructive invasion of normal organs through direct extension and spread to distant sites via the blood, lymph, or serosal surfaces. The abnormal clinical behavior of cancer cells is often mirrored by biologic aberrations such as genetic mutations, chromosomal translocations, expression of fetal or other discordant ontologic characteristics, and the inappropriate secretion of hormones or enzymes. All cancers invade or metastasize, but each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment, and study. About 1.2 million new cases of invasive cancer are diagnosed each year in the United States, and about 500,000 people die annually of the disease. Cancer is the second most deadly disease and is expected to surpass heart disease early in the twenty-first century to top that nefarious list. Over the past half century, the frequency of most cancers has been stable, but some dramatic changes have taken place (Fig. 154–1). Steady declines in stomach and uterine cancer have occurred, the latter undoubtedly due to routine cytologic screening for cervical cancer. The cause of the decline in stomach cancer is unknown. The most striking change has been the increases in lung cancer in both men and women, undoubtedly related to smoking. Other cancers with increasing mortality, particularly in the elderly, include melanoma, non-Hodgkin's lymphoma, and brain tumors. There have been speculations but little firm evidence to explain these changes. The overall mortality from cancer, particularly for those under age 65, has declined, primarily due to more effective therapy for cancers of fetal and hematopoietic origin that occur in the younger population. See Ch. 157 for more detailed treatment of cancer epidemiology.

ETIOLOGY AND PREVENTION. A broad array of agents can cause or directly contribute to a sequence of events or sensitize cells in such a way that cancer develops. The final common pathway in virtually every instance is a cellular genetic mutation that converts a well-behaved cellular citizen of the body into a destructive renegade that is unresponsive to the ordinary checks and balances of a normal community of cells. Promoters (oncogenes) and suppressors (like the retinoblastoma or *p53* gene) play a central role in many cases (see Ch. 156). Chemicals such as benzene and nitrosamines, physical agents such as gamma and ultraviolet radiation, and biologic agents such as the Epstein-Barr and hepatitis viruses contribute to carcinogenesis under certain circumstances. Evidence exists to link dietary factors to carcinogenesis; although not as clear as one would like, the evidence is strong enough to recommend diets low in fat and high in fiber. A sensible diet is based on grains, vegetables, and fruits, with smaller than the current average proportions of fat. Inherited susceptibilities are becoming more evident and probably play a key role in a significant number of cancers of the breast and colon. Down syndrome and the Li-Fraumeni syndrome are well-known harbingers of a substantial risk for developing cancer.

The single most important carcinogen in the United States and Europe is tobacco, because it causes or contributes to the development of about one-third of all cancers—primarily lung, esophageal, head and neck, and bladder. Less well appreciated is the contribution tobacco may make to causing breast, colon, and gastric cancer. Tobacco-related cancer is also important because it is preventable by the obvious, inexpensive, and 100% effective means of abstention. Although the total number of smokers in the United States has declined, through the skillful and irresponsible efforts of tobacco companies women smoke more than ever, adolescents continue to view smoking as socially chic, and the number of smokers in Asia and the third world countries is growing at an alarming rate. Cancer etiology and prevention are treated in more detail in Ch. 155.

EARLY DETECTION OF CANCER. When prevention of cancer is not possible because effective means are lacking, early detection is the next best strategy to reduce cancer mortality. The American Cancer Society (ACS) has recommended a series of cancer screening procedures for asymptomatic individuals (Table 154–1). Not all experts agree on the frequency or age ranges for employing such procedures, but the ACS recommendations are a well-considered and useful guide that, at the very least, indicates the cancers most amenable to clinically useful early detection by conventional techniques. An even more exciting development in this effort has been the emergence of genetic screening and counseling of families at high risk for developing cancer. Individuals at risk are identified largely by analysis of family pedigrees, and the increasing availability of the revolutionary tools of molecular biology can identify specific genetic mutations (see Ch. 156). As this is being written, the cloning of a mutated gene associated with a large minority of breast cancers appears imminent. It is certain that many such genes will be identified, focusing the cancer screening and early detection efforts more efficiently and productively on high-risk populations (see Ch. 155).

CANCER TUMOR GROWTH. While it is impossible to know the specific details of early *in vivo* tumor growth and the efficiency of tumor cell renewal of human cancer, clinical and laboratory observations have provided a reasonable conceptual framework. This framework should be used with caution, however, because it is certain that the intrinsic factors that control tumor growth and propagation are far more complex, episodic, and heterogeneous than we know, even within a single tumor mass. Furthermore, the stromal environment and neovascularization of tumors have become more central to our understanding of this process than heretofore. Nonetheless, the following description can be a useful reference point.

A tumor has reached the size of clinical detectability when it contains about 10^9 cells, weighing about 1 gram and occupying a volume of about 1 cc. A three-log increase to 10^{12} cells, 1 kg, and 1000 cc is often lethal. Below 10^9 cells, the tumor is usually undetectable, but it has already undergone at least 30 doublings, and only 10 further doublings will produce the 1 kg of tumor. This exercise illustrates how much has already occurred, with all the opportunities for the cancer to undergo advantageous mutation and metastasis, before clinical detection. Once the tumor has grown into the clinically evident range, it tends to grow progressively slower with increasing size. This deceleration of growth probably occurs because the tumor outgrows its blood supply, reaches anatomic boundaries, and responds to yet undiscovered feedback regulation from other members of the now larger and more heterogeneous mass of tumor cells. Thus cancers probably grow much like bacteria after inoculation into a favorable medium. The phases of bacterial growth describe a sigmoid curve (Fig. 154–2): an early lag phase of inapparent or slow growth followed by exponential growth. Growth then slows when new cell production and cell

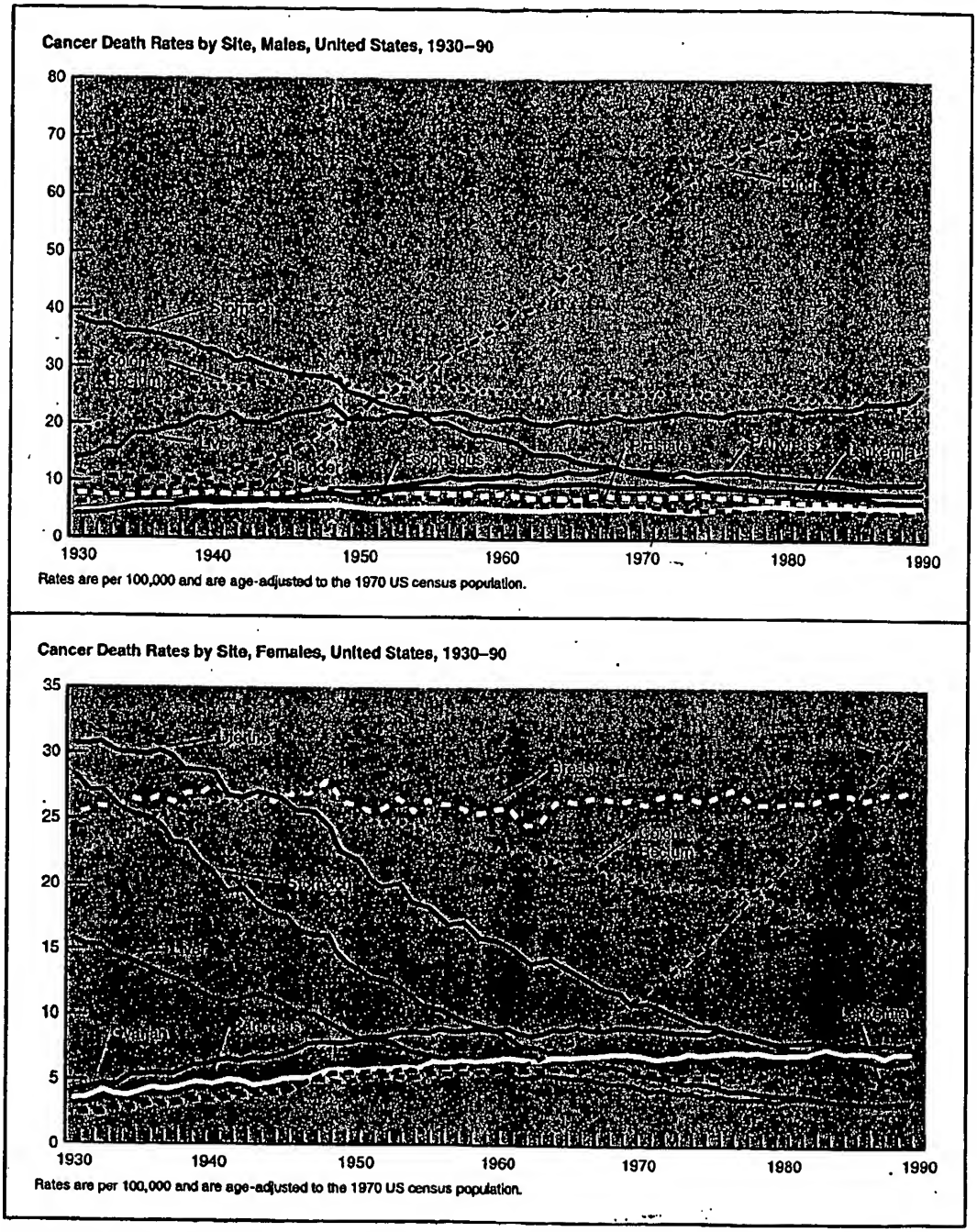

FIGURE 154-1. Cancer death rates in the United States. (From Cancer Facts and Figures—1994. Atlanta, American Cancer Society, 1994.)

death are nearly equal, with the latter phase in culture due to crowding and inadequate nutrients. Of course, in bacteria as well as cancers, the specific growth characteristics differ among types as well as within types that have developed subpopulations of mutant clones.

Most chemotherapy acts by damaging DNA, so it tends to be most effective in rapidly growing tumors such as acute leukemia, lymphomas, and testicular cancers. Also, after gross surgical removal, residual cancer cells may grow more rapidly and be more sensitive to subsequent ("adjuvant") chemotherapy. The sensitivity or resistance to chemotherapy or radiation, however, probably has as much or more to do with the specific biochemical and metabolic features of the cancer cell as with its growth characteristics (see Ch. 165).

MANAGEMENT OF THE PATIENT WITH CANCER

Oncology has been transformed over the past 40 years. From a diverse set of orphan diseases usually managed by surgeons alone and viewed with despair by most physicians, it has become a complex and exciting discipline that draws its strength from the essential partnership of specialists in medicine, surgery, pediatrics, pathology, radiation oncology, diagnostic imaging, psychiatry, and others. This remarkable evolution can be credited to therapeutic successes and biologic advances that could not be imagined in the early 1950's. At its best, oncology has pointed the way to an understanding of the biologic variability of cancer and the success that is possible with a coordinated multimodal approach to therapy.

GOALS. The oncologist—that is, anyone who seriously and expertly assumes responsibility for the management of patients with cancer—should have three sets of goals: therapeutic, human, and scientific. The initial therapeutic goal is to cure patients and return them to a normal place in society. This should be attempted in virtually all cancers, even when the likelihood of cure is small. It requires an attitude of reasonable hope and determination as well as a willingness to attempt difficult, dangerous, and sometimes daring approaches to fundamentally resistant diseases. If after a reasonable

TABLE 154–1. SUMMARY OF AMERICAN CANCER SOCIETY RECOMMENDATIONS FOR THE EARLY DETECTION OF CANCER IN ASYMPTOMATIC PEOPLE

Test or Procedure	Population		
	Sex	*Age*	*Frequency*
Sigmoidoscopy, preferably flexible	M & F	50 and over	Every 3–5 years
Fecal occult blood test	M & F	50 and over	Every year
Digital rectal examination	M & F	40 and over	Every year
Prostate examination*	M	50 and over	Every year
Papanicolaou test	F	All women who are or who have been sexually active, or have reached age 18, should have an annual Papanicolaou test and pelvic examination. After a woman has had three or more consecutive satisfactory normal annual examinations, the Papanicolaou test may be performed less frequently at the discretion of her physician.	
Pelvic examination	F	18–40	Every 1–3 years with Papanicolaou test
		Over 40	Every year
Endometrial tissue sample	F	At menopause, if at high risk†	At menopause and thereafter at the discretion of the physician
Breast self-examination	F	20 and over	Every month
Breast clinical examination	F	20–40	Every 3 years
		Over 40	Every year
Mammography‡	F	40–49	Every 1–2 years
		50 and over	Every year
Health counseling and cancer checkup§	M & F	Over 20	Every 3 years
	M & F	Over 40	Every year

From Cancer Facts and Figures—1994. Atlanta, American Cancer Society, 1994.

* Annual digital rectal examination and prostate-specific antigen should be performed on men 50 years and older. If either is abnormal, further evaluation should be considered.

† History of infertility, obesity, failure to ovulate, abnormal uterine bleeding, or unopposed estrogen or tamoxifen therapy.

‡ Screening mammography should begin by age 40.

§ To include examination for cancers of the thyroid, testicles, prostate, ovaries, lymph nodes, oral region, and skin.

attempt permanent cure is not possible, the physician must not abandon the patient but should aim for a secondary goal, a long, qualitatively satisfactory remission. If this is no longer possible, the tertiary level of therapeutic intent is to obtain a remission of any kind and duration; however, at this stage and later, one is less willing to expose the patient to the possibility of serious side effects or long hospitalization. When the possibility of remission of any type becomes remote, the goal at the fourth level is to control the disease and symptoms by the judicious use of palliative therapeutic measures.

The objective in the final stage is terminal care, which is always difficult because it requires the admission that specific therapy is no longer of any value. The only goal now is to provide comfort. Instead of blood transfusions, antibiotics, or chemotherapeutic agents, the physician must use pain medications, sedation, psychosocial support, and other comfort measures with the thought of returning the patient to the home or other appropriate setting and to the support of family.

The human goals in oncology are inextricably linked with the therapeutic and scientific goals. Physicians, nurses, and other health care providers wish to cure patients or improve their conditions so that they may fulfill their human destiny as well as possible. This requires sensitivity to the particular needs of the patient and family and an understanding of the social environment from which they came and to which they must return. The physician must help them maintain their dignity, understand their weaknesses, and refuse to allow any frustration, animosity, or excessive friendship to develop and threaten good judgment and the best interests of the patient.

The use of scientific methods in oncology is only in its adolescence, and definitive treatment has been established for only a small proportion of the circumstances and types of cancers that can arise. Systematic protocol studies yield useful information about a new drug, a novel regimen, or a biologic feature. Presentation and criticism of one another's efforts in a collegial and scientific manner are essential to advancing the knowledge about a particular treatment. Physicians who manage a small number of patients per year cannot possibly have the background and support necessary to treat these complex diseases adequately. This task is best left to specialists who participate in active scientific programs and have the resources to deliver optimal clinical care. It is also important to understand the limitations of science and that at times no treatment is the best option.

DIAGNOSTIC PRINCIPLES. The first diagnostic principle is that adequate tissue must be obtained from the tumor to establish the specific diagnosis and subtype of cancer. The rare exceptions are instances in which a biopsy might be life-threatening and the anatomic location is virtually pathognomonic of a specific histology. Some brain tumors and anterior mediastinal tumors that compress the trachea and blood vessels are two notable examples. In the latter situation, often due to a lymphoma, steroids may reduce the tumor size and relieve symptoms before a biopsy is attempted. More often, an adequate sample must be obtained before therapy is started unless complete surgical excision is definitively diagnostic and therapeutic. Because management of each type and subtype of cancer is often distinctive, every effort must be made to obtain appropriate samples, even if therapy is delayed for a short time. A specific diagnosis is seldom a problem in the leukemias because bone marrow aspiration usually affords a ready answer; the solid tumors present the greater difficulty.

Cancer diagnosis may be challenging and urgent; an understanding of some of its unusual manifestations can be very helpful. Elsewhere in this text, sound guidance is provided on paraneoplastic syndromes (see Ch. 158), endocrine manifestations of cancer (see Ch. 159), cutaneous manifestations of cancer (see Ch. 161), and oncologic emergencies (see Ch. 163).

A second diagnostic principle is to establish the extent of the disease. In the leukemias, this can be readily accomplished by physical examination, routine laboratory tests, chest roentgenography, and examination of cerebrospinal fluid. With solid tumors, determining the extent of the disease, that is, the *stage* of the tumor, often involves major surgery and an extensive examination that uses diagnostic imaging techniques. A coordinated approach involving the surgeon and pathologist is crucial to determine the extent of tumor invasion; without this approach, one may lack essential information for planning treatment and for judging its success. Failure to detect

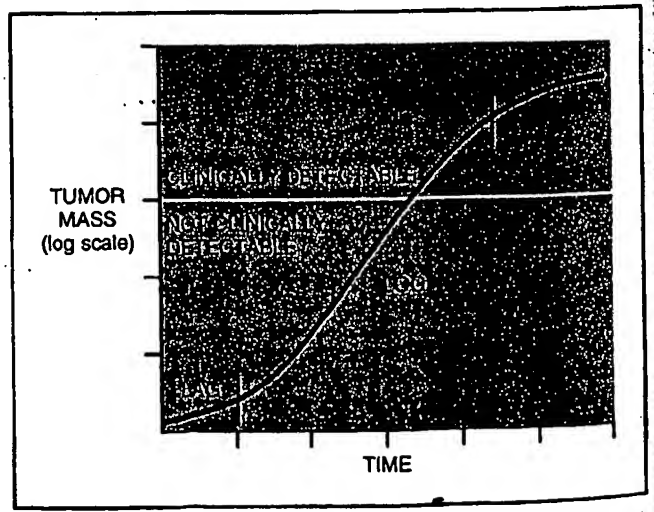

FIGURE 154–2. A schematic representation of the phases of growth of a cancer. After a period of inapparency (lag phase), growth tends to be logarithmic, followed by deceleration due to inadequate nutrients, competitive inhibition among cells, or a lack of neovascularization. (This resembles the growth of bacteria inoculated into a favorable medium.) The tumor has gone through many doublings before it becomes clinically apparent.

a tumor that has extended to regional lymph nodes can lead to undertreatment and a false impression that the local treatment, whether surgery or radiation therapy, was adequate. A simplified generic staging system is shown in Table 154–2. More detailed and specific staging systems have been developed for most cancers that take into account peculiar pathogenetic features, modes of spread, and potential curability. In addition, modern oncology demands an extensive biologic classification of leukemias and solid tumors, often requiring sophisticated scientific approaches not available a few years ago. This includes the use of monoclonal antibodies to determine the phenotype of lymphomas and leukemias, light and electron microscopy with special stains to determine the presence of glycogen, enzymes, or other substances that help to classify solid tumors, chromosomal analysis and modern molecular probes that identify unique characteristics of a disease, and responsible oncogenes, suppressor genes, and familial genes (see Ch. 156 and 158).

THERAPEUTIC PRINCIPLES. The first step in treatment is to know the patient. All pertinent information—medical, developmental, and social—must be sought before treatment is planned. The second step is to know the tumor: its usual behavior, usual rate of growth, mode of spread, whether it is local or systemic, and any features that may provide prognostic or therapeutic leads. Third, one must know the available therapies: not only the therapeutic modalities such as chemotherapy, radiation therapy, and surgery but also the skills and limitations of colleagues. Finally, one must know oneself: one's skills, experience, objectivity, and limitations. All these factors shape decisions concerning the patient. Treating patients with cancer is not easy; one must be prepared for losses as well as gains while keeping overall progress and success in mind.

As indicated above, clarity of intent—whether curative, palliative, or supportive—will avoid the confusion of approach and method. Treatment protocols—either research or "standard of care" regimens—are important tools in this regard because they allow strategies to be planned should any momentary decisions be necessary. Protocols are also more likely to provide useful conclusions from a study or experience, because a scientific question or a uniform approach has been formulated and data have been collected in a systematic manner. A protocol is, however, only a road map. The planned therapy may require adjustment if complications develop after treatment has begun. Although many of these adjustments can be anticipated and specified in the protocol, not every circumstance can be foreseen. A protocol is also intended to provide practical information that will lead to improved treatment of subsequent patients.

THERAPEUTIC MODALITIES. There are four principal therapeutic modalities for cancer. *Surgery* is the oldest and most definitive when the tumor is localized under the most favorable anatomic circumstances. For example, for a small tumor localized in the breast, the interior of one kidney, or the peripheral edge of the liver, surgery is usually definitive, curative, and leaves no undue side effects. For many solid tumors, however, surgery alone is inadequate because of local or distant spread. Surgery is also crucial in establishing the extent of a tumor. Considerable surgical skill and experience are required to approach a tumor that may or may not be resectable, achieve tumor-free margins, and obtain the necessary tissue without causing further dissemination.

Radiotherapy is most useful for localized tumors that cannot be resected at all or without serious morbidity and for tumors, such as Hodgkin's disease, that tend to spread to predictable contiguous sites. Therefore, a port of radiation can be enlarged beyond the known extent of the tumor and be quite effective. Unfortunately, radiotherapy can have serious side effects, especially in children who are growing and developing. Nonetheless, the skilled use of radiotherapy is an essential part of oncology; as with all modalities, its role changes depending on new knowledge about a particular tumor. The dosage of radiotherapy is based on an estimate of the dose absorbed by tumor, measured in equivalent units called "centigrays" (cGy) or "rads."

Chemotherapy was the first systemic treatment for any cancer. It most often consists of a combination of drugs, which is almost always more effective than the sequential use of single agents. Since tumors develop subpopulations of cells that differ in their sensitivity to antineoplastic drugs, combinations of agents destroy more cells more rapidly, thereby reducing the frequency of emergence of resistant clones. The mechanisms of action of common chemotherapeutic agents differ widely, although DNA damage is the common final pathway. Toxicity also differs among agents; myelosuppression and gastrointestinal disorders are the most common disturbances. Although toxicity is a concern, for many cancers the best therapeutic results depend on the intensity of the dosage; that is, effective agents given at higher doses over a shorter period are more efficacious than less intensive regimens. One must straddle the fine line between too much and too little.

Chemotherapy is used (1) as a definitive treatment, as in leukemia and some lymphomas; (2) as a principal form of treatment, as in testicular cancer and Ewing's sarcoma; or (3) as an adjuvant to another modality, such as amputation for osteosarcoma or surgical resection for breast or bowel cancer.

Biologic therapy for cancer includes, in addition to bone marrow transplantation, the newer uses of biologic response modifiers such as lymphokines or monoclonal antibodies and agents such as retinoic acid that may cause tumor cells to undergo differentiation and become harmless. These approaches, although still under development, show promise for the future.

The success of cancer therapy often depends on the skillful combination of two or more treatment modalities necessitating close cooperation of medical specialists. Failure to coordinate the effort may lead to the use of modalities in a useless or harmful sequence with an ineffective result.

Supportive care encompasses skilled general medical care. It includes management of infectious, metabolic, and cardiopulmonary disorders that frequently occur in patients undergoing aggressive treatment or surgical procedures. The judicious use of blood products is an essential part of supportive care, and infectious complications in the immunosuppressed patient must be anticipated. Because infections account for a large proportion of hospitalizations and deaths in patients with cancer, one cannot provide modern therapy without appropriate support from specialists in infectious diseases.

MEASURES OF SUCCESS. The measures of success in the treatment of patients with cancer are relatively simple, although not always precise. The first is survival without recurrence of tumor. Unfortunately, some malignancies recur many years after apparently successful control. An operative definition of cure, therefore, differs for each cancer. A patient who remains tumor-free for 2 years after completing therapy is probably cured if the tumor was neuroblastoma, lung cancer, acute myeloid leukemia, or lymphoblastic lymphoma. A much longer period would be needed to conclude a cure for breast cancer, Ewing's sarcoma, Hodgkin's disease, or acute lymphoblastic leukemia of childhood.

The second measure of success is resumption of a normal life pattern without sequelae from the disease or its treatment. The Karnofsky scale (Table 154–3) is a useful guide to measure "performance status." Unfortunately, late side effects, such as second malignancies, may occur 10 to 15 years after treatment is completed. A good estimate of success and failure is usually apparent in a few years, but long-term follow-up of patients is essential for definitive answers.

TABLE 154–2. SIMPLIFIED GENERIC CANCER STAGING SYSTEM

Stage 1	Localized. Usually confined to the organ of origin. Usually curable with locally effective measures such as surgery or irradiation.
Stage 2	Regional. Extends beyond organ of origin but remains nearby, in lymph nodes, for example. Often curable by local measures alone or in combination (surgery ± irradiation) or by a local modality with chemotherapy.
Stage 3	Extensive. Has extended beyond regional site of origin, crossing several tissue planes or extending more distantly via lymphatics or blood. Also may be confined to an organ or region, but be unresectable because of anatomic extent or location. This stage is used rather than stage 2 or stage 4 depending upon the usefulness of local and systemic treatment modalities and the likelihood of cure for that specific cancer.
Stage 4	Widely disseminated. Often involves the bone marrow or multiple distant organs. Rarely curable with current armamentarium.

TABLE 154–3. PERFORMANCE STATUS (KARNOFSKY SCALE)

Criteria of Performance Status (PS)		
Able to carry on normal activity; no special care is needed	100	Normal; no complaints; no evidence of disease
	90	Able to carry on normal activity; minor signs or symptoms of disease
	80	Normal activity with effort; some signs or symptoms of disease
Unable to work; able to live at home and care for most personal needs; a varying amount of assistance is needed	70	Cares for self; unable to carry on normal activity or to do active work
	60	Requires occasional assistance but is able to care for most needs
	50	Requires considerable assistance and frequent medical care
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly	40	Disabled; requires special care and assistance
	30	Severely disabled; hospitalization is indicated although death not imminent
	20	Very sick; hospitalization necessary; active supportive treatment is necessary
	10	Moribund, fatal processes progressing rapidly
	0	Dead

PATIENT-FAMILY-PHYSICIAN RELATIONSHIP. Patients with cancer and their families face an extremely difficult time. They need a physician who is hopeful, truthful, compassionate, understanding, accessible, informative, and knowledgeable. Although cancer patients understand that several physicians and other professionals will be involved in their care, they prefer and need one physician who can assume ultimate responsibility for their myriad needs.

Patients should be told of plans and procedures in language that is understandable and appropriate. Some idea of the nature of cancer can be provided by analogy. For example, one may compare leukemia to the overgrowth of a farmer's field (bone marrow) by weeds (leukemia cells) that prevent the growth and export of crops (normal blood cells). Because the weeds cannot be removed manually from the marrow, chemicals are used to destroy the weeds and allow the crops to grow.

Physicians and family often mistakenly believe that the patient is only concerned with the possibility of death. In fact, patients are often equally or more concerned with the immediate implications of disease, for example, separation from family, pain, disfigurement, lengthy hospitalization, financial ruin, or missed time at work or school. Sensitive caregivers will understand and try to address these issues. Some patients and families become very knowledgeable about the disease and in fact may know as much as or more than physicians about certain details; this should be viewed as an asset that can aid the physician in management. Physicians, nurses, and other caregivers may become emotionally attached to a patient or the family. This need not be avoided as long as the necessary professional relationship and sound medical judgment are sustained. The physician must realize that above all the patient and family want an expert physician, not a pal or buddy.

When the cancer becomes resistant to therapy and death is imminent, the patient and family need support more than ever to help them through the last days. The family must understand that no known effective therapy remains and that the goal of management must change from destroying cancer cells to providing comfort. Once this is decided, chemotherapy, transfusions, antibiotics, blood counts, and other laboratory tests are no longer necessary. The patient needs to be hospitalized only if proper supportive care or pain medication cannot be given at home. For pain that cannot be controlled by oral analgesics, parenteral morphine is the drug of choice and is most effective when given by continuous intravenous infusion. The inadequate control of cancer pain in the United States is a national scandal. The demonstrably unwarranted fear of narcotic addiction, the rigid adherence to timed dosages irrespective of need, and the lack of knowledge and plain human sensitivity of doctors and nurses are widespread and indefensible. There is no reason for any cancer patient to suffer severe unremitting pain, a consequence of cancer more feared than death by most patients. Very effective narcotic regimens, including self-regulated intravenous drips, are both safe and readily available.

Patients themselves seldom ask the physician at this time whether they are going to die, probably because they already know or suspect the truth and do not want to confront the physician with an uncomfortable question. Should the question be asked, however, the patient probably knows the answer already; to deny this is worse than useless. Although guidelines can be provided for caring for patients during this difficult period, the medical staff must adopt an approach that is suitable to the particular patient and circumstances. Most of all, the patient needs palpable demonstration that the medical staff is readily available and willing to listen, to comfort, to provide any possible service, and simply to be there. Even patients who are at home should not be abandoned; telephone communication can provide welcome support to the family. Both hospice care and home visits by nurses can be a godsend to patients and their families.

155 CANCER PREVENTION

Gilbert S. Omenn

Cancers are diagnosed in 1.2 million people in the United States and claim over 500,000 lives each year, one fourth of all deaths. Fear of cancer, suffering from cancers and their treatment, and the limited benefit of treatments for most common cancers combine to make prevention an increasing priority in clinical medicine and in public health.

As Figure 155–1 shows, the leading cancer killer by far in both men and women is lung cancer, followed by cancers of the prostate, colon and rectum, and pancreas in men and by cancers of the breast, colon and rectum, ovary, and pancreas in women. Pancreatic and pulmonary cancers are particularly lethal.

The primary modalities for cancer prevention (see Table 155–1) involve behavior change, including smoking, alcohol, diet, and physical activity. Reduction of exposures to carcinogenic agents from all environmental sources comes next. Under intensive investigation are hormonal, nutritional, and pharmacologic interventions and genetic screening, counseling, and eventual treatments for those with testable inherited predispositions.

HEALTH-PROMOTING/CANCER-PREVENTING BEHAVIOR CHANGES

SMOKING CESSATION AND SMOKING PREVENTION. Diseases related to cigarette smoking represent a twentieth-century epidemic, now spreading globally. Smoking is the primary cause of cancers of the lung, larynx, oral cavity, and esophagus (approximately 10 to 20 times the risk compared with nonsmokers) and contributory to cancers of the pancreas, bladder, kidney, stomach, and cervix and to leukemia (about 2 times the risk). Smoking acts synergistically with chemical and radiation carcinogens in the lung and with alcohol in the esophagus and oral cavity. Former smokers, after a lag of up to 4 years, show a progressively lower relative risk compared with continuing smokers and even compared with the slowly rising rate as never-smokers age. However, the absolute risk of lung cancer probably never declines, in sharp contrast with coronary heart disease endpoints. Low-tar, low-nicotine, and filtered cigarettes have had little or no protective effect, because the smokers tend to inhale more deeply and more frequently.

Snuff dipping and smokeless tobacco have been promoted successfully to adolescents in recent years; their predisposition to cancer is similar to that of inhaled smoking. Leukoplakia, a white patch involving the oral mucosa epithelium, is a telltale premalignant lesion found in up to half of tobacco chewers, with a 5% risk

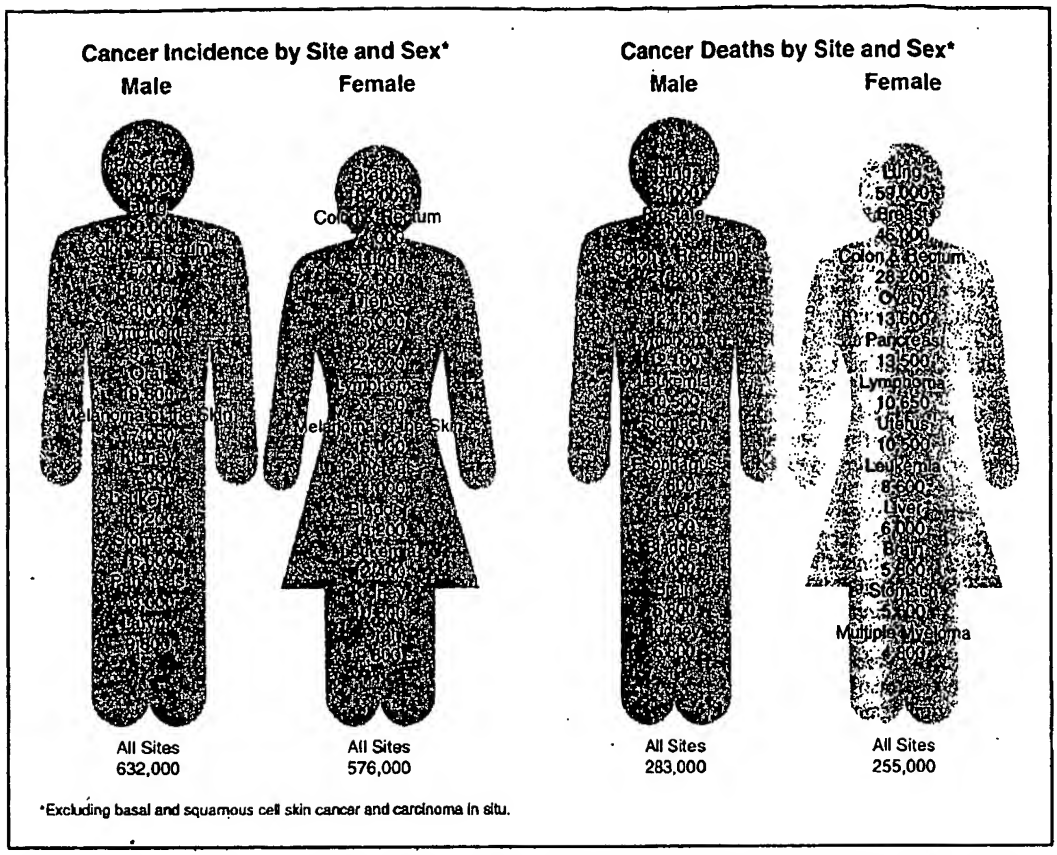

FIGURE 155–1. Leading sites of cancer incidence and death—1994 estimates. (From Cancer Facts and Figures—1994. Atlanta, American Cancer Society, 1994.)

of epidermoid carcinoma. Finally, environmental tobacco smoke (ETS), or second-hand smoke, has been declared a definite human carcinogen by the Environmental Protection Agency; 6000 cases of lung cancer per year are attributed to ETS by the National Research Council.

A huge literature attests to the difficulty of helping smokers quit. About 5% "quit" by themselves (for at least a 6-month period) each year, but others relapse. Physicians play a key role in urging smokers to quit and in guiding them to self-help materials, classes, or pharmacologic quitting aids. Work-site, family, and community reinforcement is essential; increased taxes on tobacco products reinforce as well. Prevention of smoking, especially in young people, minorities, and women, can be enhanced by organized community and school programs as well as regulatory actions.

MODERATION OF ALCOHOL INTAKE. The National Cancer Institute *Dietary Guidelines* recommend that consumption of alcoholic beverages, if any, should be moderate. Alcohol intake is highly associated with cancers of the esophagus, oral cavity, pharynx, and larynx and, less strikingly, with liver, rectal, pancreatic, and breast cancer. It acts synergistically with cigarette smoking.

DIET. Guidelines for healthy diets strongly recommend decreases in fat and increases in fiber intake, most easily described as "five-a-day" fruits and vegetable portions. Such advice aims at preventing cancers, heart disease, and bowel disorders too.

The typical U.S. diet has 39% of calories from fat or about 150 grams per day. Dietary fat intake correlates positively with incidence and mortality rates for breast, prostate, and colon cancers. International, migrant, and time-trend data indicate that reduction in dietary fat to 20% of caloric intake would reduce breast cancer risk by two thirds. Unfortunately, most case-control (retrospective) and cohort (prospective) epidemiologic studies have found less striking correlations or none at all. Similar inconsistencies underlie positive associations of fat intake with colorectal and prostate cancers. Fat intake involves many variables, including percentage of calories, grams per day, saturated versus unsaturated fats and fatty acids, overweight, and duration of diet. Each type of cancer possesses other confounding or interacting risk factors. Experimental studies in rodents show that dietary fat may exert tumor-enhancing or -promoting effects on the breast directly through changes in cell membranes or indirectly through neuroendocrine systems. In the colon, fat may influence bile acids, sterol substrates, and fecal microflora.

Clinical trials are essential to test hypothesized mechanisms and behavior change for cancer prevention. A feasibility study for the Women's Health Trial showed that women aged 45 to 69 can lower mean dietary fat intake to below 25% of energy requirements and maintain the diet and good health for 2 years. Reduction in dietary fat intake is a major component of the Women's Health Initiative, a massive trial aimed at reducing breast cancer, heart disease, and osteoporosis in postmenopausal women.

INCREASE IN DIETARY FIBER. The surgeon Dennis Burkitt deduced from widely varying country rates for colon cancer that

TABLE 155–1. PROPORTIONS OF CANCER DEATHS ATTRIBUTED TO VARIOUS RISK FACTORS

Factor or Class of Factor	Best Estimate	Range of Estimates
Tobacco	30	25–40
Alcohol	3	2–4
Diet	35	10–70
Food additives*	<1	−5–2
Reproductive/sexual behavior	7	1–13
Occupation	4	2–8
General pollution	2	1–5
Industrial products	<1	<1–2
Medicines/medical procedures	1	0.5–3
Geophysical factors†	3	2–4
Infections	≈10?	1–?

* Minus indicates potential benefits from antioxidants and other additives.
† UV and cosmic radiation included; perhaps 1% truly avoidable.
From Doll R, Peto R: The causes of cancer: Quantitative estimates of avoidable risks of cancer in the United States today. J Natl Cancer Inst 66:1193, 1981.

fiber-rich diets play a protective role. The highest rates occur in western countries with a high intake of refined carbohydrates compared with the naturally occurring fiber-rich foods common in African and Asian countries, where colon cancer rates are low. Low colon cancer rates with a mean intake of 31 grams of fiber per day in Finland contrast with high rates in Denmark and New York on 17 grams of fiber per day despite similar fat intakes. Fiber describes a heterogeneous category, defined by plant origins and resistance to digestion by human enzymes, making measurement awkward. Soluble fibers (gums, mucilages, pectins, and hemicelluloses) delay gastric emptying, slow glucose absorption, and lower serum cholesterol, with lesser effects on bulk and transit time. Insoluble fibers (cellulose, lignin, other hemicelluloses) increase fecal bulk and decrease intestinal transit time. Whole-grain breads, cereals, fruits, vegetables, legumes, and nuts contain lots of fiber but provide fibers of markedly different natures. Cellulose and hemicellulose are found primarily in cereals and grains; lignin, primarily in berry fruits; and pectin, in citrus fruits and apples.

Dozens of epidemiologic studies give consistent findings of a moderate-to-strong protective effect of fiber against colon cancer, as well as a protective effect of vegetables. When one analyzes the different forms of fiber or foods rich in fiber, however, more variable results are obtained. One should remember that no effect of a dietary component can be identified unless there is sufficient variation in intake within the population studied.

INCREASED PHYSICAL ACTIVITY. Overcoming sedentary or inactive lifestyles benefits cardiovascular, respiratory, muscular, cognitive, and metabolic systems. Increased physical activity seems to offer significant protection against colon cancer.

REDUCTION IN EXPOSURES TO ENVIRONMENTAL CARCINOGENIC CHEMICALS. Asbestos fibers, inorganic arsenic compounds, bis-chloromethyl ether, chromium compounds, mustard gas, nickel dusts, and polycyclic aromatic hydrocarbons from coal and gasoline combustion are lung carcinogens; vinyl chloride causes a distinctive angiosarcoma of the liver; some pesticides are associated with the development of non-Hodgkin's lymphoma; aromatic amine dyestuffs can cause bladder cancer; leather production and isopropyl alcohol manufacturing are associated with nasal cancers; and benzene can cause acute myelocytic leukemia. Tobacco smoke is the most prevalent chemical carcinogen, possibly followed by charbroiling of meats and fish.

PHYSICAL AGENTS. Ultraviolet radiation is the primary cause of skin cancers, including melanoma and lip cancer. Ionizing radiation (including radiotherapy) increases rates at essentially all exposed sites. Nonionizing radiation and electromagnetic fields have been suspected of increasing leukemia and brain cancer and possibly breast cancer rates, but the data are not consistent and the relationship is far from demonstrated.

DRUGS. Alkylating agents can cause leukemias; androgen anabolic steroids, liver cancer; chlornaphazine, bladder cancer; estrogens (possibly also "environmental estrogens"), cancers of the vagina and cervix (diethylstilbestrol), endometrium (postmenopausal estrogens), or liver and cervix (steroid contraceptives); azathioprine and cyclosporine immunosuppressants, non-Hodgkin's lymphoma; and phenacetin-containing analgesics, renal pelvic tumors.

INFECTIOUS AGENTS. Specific infectious agents can cause several cancers: primary hepatocellular cancer is associated, with hepatitis B and C (with distinctive mutations in gene *p53* and with synergistic effects of aflatoxins derived from *Aspergillus flavus* growth on crops); cervix, with certain human papillomaviruses; Burkitt's lymphoma and nasopharyngeal, with Epstein-Barr virus; Kaposi's sarcoma and non-Hodgkin's lymphoma, with HIV-1; T-cell leukemia, with HTLV-I; urinary bladder *(Schistosoma haematobium)* and cholangiocarcinoma of the liver *(Clonorchis sinensis)*, with parasites; and gastric cancer, with *Helicobacter pylori*. Environmental or antibiotic control of these infections and/or vaccines to protect against exposure can be effective. Population-wide neonatal hepatitis B virus immunization is expected to reduce or eliminate the scourge of primary liver cancer in Taiwan.

CANCER PREVENTION INTERVENTIONS

CHEMOPREVENTION. Population trials of chemopreventives are currently under way worldwide. Because of their apparent antioxidant, tumor suppressor, and immunomodulatory actions, micronutrients (especially carotenoids and retinoids) have been prime agents, based on observational epidemiologic work as well as animal and cell culture findings showing protective effects. Other antioxidants (vitamins E and C and selenium), anticarcinogens in soybeans (protease inhibitors, isoflavones, and phytosterols), and inhibitors of cellular proliferation or tumor promotion are in phase I and phase II studies. For example, calcium supplementation and possibly aspirin and other nonsteroidal anti-inflammatory agents can reduce colonic cell proliferation in humans.

The largest current studies involve beta-carotene alone (22,000 male physicians), beta-carotene plus vitamin E (29,000 male smokers in Finland), beta-carotene plus vitamin A (14,000 male and female U.S. smokers and 4000 asbestos-exposed workers), and beta-carotene plus vitamin E plus aspirin (40,000 female health professionals). The first large trial to report its findings shocked the medical and vitamin supplement worlds. In April of 1994, the Alpha-Tocopherol/Beta-Carotene study in Finland reported not only no benefit from vitamin E or from beta-carotene but also 18% lung cancer and 8% overall mortality rate increases (both statistically significant) in the men receiving beta-carotene, 20 mg per day. This unexpected and unexplained result firmly demonstrates that seemingly logical approaches must be tested in randomized, clinical preventive trials before their merits are accepted. We await results from the other trials.

HORMONES. Cancers of the hormone-responsive tissues account for 20% of male and more than 40% of female newly diagnosed cancers in the United States. Thus chemoprevention with "antihormones" represents a promising approach. Progesterone is the prototype. Oral contraceptives (OC's) have become potent cancer prevention agents, once the early sequential OC's (which increased endometrial cancer risk) were replaced with estrogen-progesterone combinations. Women with 6 or more years of OC use have less than one-sixth the risk of endometrial cancer compared with never-users, and the effect lasts at least 15 years after discontinuation of the OC's. Combination OC's also suppress gonadotropin levels and ovulation, thereby decreasing the risk for epithelial ovarian cancers by about 40%, independent of parity. The breast is different: Progesterone increases the rate of cell division beyond that induced by estrogen. Combination therapy is now also preferred for postmenopausal hormone replacement therapy.

A strategy in premenopausal women for gaining the benefits of the OC's while actually reducing breast cancer (and cardiovascular) risk involves use of luteinizing hormone–releasing hormone (LHRH) antagonists, a "reversible bilateral oophorectomy," plus low-dose estrogen to overcome hypoestrogenic effects plus a quarterly progestogen. Antiestrogenic agents, such as tamoxifen, also are being subjected to multiple-endpoint trials.

Diethylstilbestrol and LHRH agonists are effective therapeutically against metastatic prostate cancer by reducing testosterone-mediated maintenance of prostate tissue. Inhibitors of 5-α-reductase may become useful in high-risk patients or even in primary prevention.

GENETIC SCREENING. Molecular studies in cancer reveal numerous oncogenes, tumor-suppressor genes, genes affecting cell division, cell cycle, and cell proliferation, and a host of other potential targets for cancer prevention. Known inherited cancer syndromes, such as retinoblastoma and polyposis coli, have specific mutations of general interest in carcinogenesis. If and when highly predisposing breast cancer gene(s) and cell-cycle/tumor-suppressor genes (such as the already discovered multiple-tumor-suppressor [MTS-1] p16 mutant) can be identified and converted into diagnostic tests, genetic screening and counseling programs are bound to increase. The discovery of other genetic mechanisms will bring new types of interventions as well.

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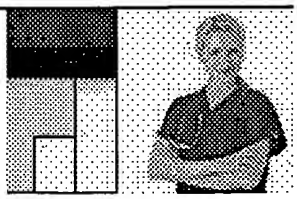

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Breast **cancer** patients, individuals at risk for osteoporosis, and individuals undergoing certain types of **bone cancer** therapies often take drugs that contain bisphosphonates. Bisphosphonates may place patients at risk for developing osteonecrosis of the jaws (a rotting of the jaw bones), according to a case report and literature review that appeared in the May/June 2006 issue of General Dentistry, the Academy of General Dentistry's (AGD) clinical, peer-reviewed journal.

Bisphosphonates are a family of drugs used to prevent and treat osteoporosis, multiple myeloma, Paget's disease (**bone** cancers), and **bone** metastasis from other cancers. These drugs can bond to **bone** surfaces and prevent osteoclasts (cells that breakdown **bone**) from doing their job.

"Healthy bones constantly rebuild themselves," explains co-author of the report Sally-Jo Placa, DMD, MPA. "However, since the jawbones have rapid cell turnover, they can fail to heal properly in patients taking any of the bisphosphonate drugs. Patients need to be aware of the possibility of complications from dental surgery or extractions." Since these drugs linger

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in the **bone** indefinitely, they may upset the cell balance in how the jaws regenerate and remove unhealthy **bone**.

In their report, the authors refer to the case of a woman who received bisphosphonate therapy intravenously to treat metastatic breast **cancer**. She then developed osteonecrosis in her upper and lower jaws following tooth removal.

"This type of osteonecrosis has been occurring since the advent of these drugs," explains co-author Wellington S. Tsai, DMD. "At this time osteonecrosis as a result of bisphosphonate therapy has **no** treatment."

Patients who are taking bisphosphonates should inform their dentist to prevent complications from dental surgical procedures. "By informing your dentist that you are taking a bisphosphonate, different avenues for treatment can be explored," says the report's third co-author Kayvon Haghighi, DDS, MD.

"It is strongly recommended that patients scheduled to receive bisphosphonate therapy should visit a dentist or an oral surgeon so problematic teeth can be treated prior to the start of therapy," the authors state.

"Widespread use of bisphosphonates to prevent or treat early osteoporosis in relatively young women and the likelihood of long-term use is a cause for concern," says Dr. Placa. "How bisphosphonates interfere with healing after dental surgery is still unclear and further research will be needed. It is imperative that the public understands there is **no** present treatment or **cure** for this problem."

Tips to reduce the risk for osteonecrosis of the jaw and maintain a healthy mouth:

* Inform your general dentist or specialist if you are taking bisphosphonates.
* Check and adjust removable dentures.
* Obtain routine dental cleanings.
* Opt for root canal therapy over extractions when possible.

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Paget's osteosarcoma - no cure in sight

Authors: Shaylor, Phillip J.; Peake, David; Grimer, Robert J.; Carter, Simon R.; Tillman, Roger M.; Spooner, David

Source: Sarcoma, Volume 3, Numbers 3-4, 1 December 1999, pp. 191-192(2)

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Abstract:

Purpose Paget's osteosarcoma has a fearful reputation with a quoted survival of at best 5% at 5 years. We therefore reviewed our experience of 26 patients treated over the last 25 years using modern staging and limb salvage techniques to see if there had been any improvement in survival. Subjects: We identified 26 patients on the Royal Orthopaedic Hospital Oncological database with a diagnosis of sarcoma secondary to Paget's disease. Results: The survival rate was 53% at 1 year, 25% at 2 years and no patient survived for 5 years. The median survival was 21 months for those treated with curative intent and 7 months for those treated palliatively. Four of the five patients treated with limb-sparing surgery developed local recurrence between 5 and 12 months, the fifth died at 14 months. There was no difference in survival between amputation and limb salvage. Discussion: The development of sarcomatous change in Paget's disease is well recognised. It represents an important segment of primary bone tumours in patients over 40 years of age. The prognosis is appalling. Indeed only 15 of 368 cases (4%) from a number of historical series have survived more than 5 years. Our results are similarly disappointing with no survivors at 5 years despite modern methods of management of bone tumours. While there is no difference in local recurrence rates or survival between limb reconstruction and limb ablation the poor prognosis for both means that neither can be recommended at present. Sarcomatous change in Pagetoid bone should therefore be regarded as a different disease to primary osteosarcoma. It remains an incurable disease with a poor prognosis.

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